Regeneration Yesterday and Today

Principles of Regenerative Biology
Bruce M. Carlson
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Regeneration is one of a small number of scientific problems that immediately excite lay people. When they hear that a salamander can regenerate a missing leg, they invariably respond, "That's amazing. How come they can do it and we can't? Will we ever be able to do it?" Unlike some other areas of developmental biology, which have become very detailed and technical, regeneration still involves some real unknowns, not least of which is the answer to this typical lay person's question. So it is not surprising that every grant application to work on regeneration hints at some point that human appendage regeneration may one day be possible.

Bruce Carlson's new book, *Principles of Regenerative Biology* (Figure 1), provides a great opportunity to ask how much we really know about regeneration and how much still lies in the black box. The book has a wide scope, effectively attempting to cover all regenerative phenomena in animals. Although some books specifically on limb regeneration have appeared in recent decades, I believe this is the first general monograph on the subject since that of Goss (Goss, 1969). It contains a great deal of very interesting material, and even an old soldier like myself was able to find some things that I had never encountered before (for example, the catfish barbel story and the Ilizarov technique for lengthening bones).

Carlson takes a broad view of what may be called regeneration and allows cells, tissues, or body parts into his book so long as they are capable of growing back after removal. So he includes much material about such topics as mammalian muscle repair and axonal regeneration, as well as classical topics such as the urodele limb and the planarian worm. He is unusual among Western scientists in reading Russian and being familiar with the Soviet regeneration literature, which contain interesting material, especially from the 50s and 60s, when there was a focus on studying regenerative events in mammals.

Perhaps because the book has "principles" in its title, it is presented in terms of a theme for each chapter, such as "tissue interactions," "the substrate," "reintegrative processes," and "influence of the environment." This has the consequence that the same phenomenon, such as limb or axonal regeneration, is usually discussed several times in the book in relation to each of these themes, which sometimes seem rather similar to each other. I think I should have preferred a more conventional taxonomic presentation, which would make it easier to find what you are looking for, but I accept that different people like to do things different ways. Apart from these themed chapters, the book also includes chapters dealing with such hot topics as stem cells, tissue engineering, and the effects of aging on regeneration and repair.

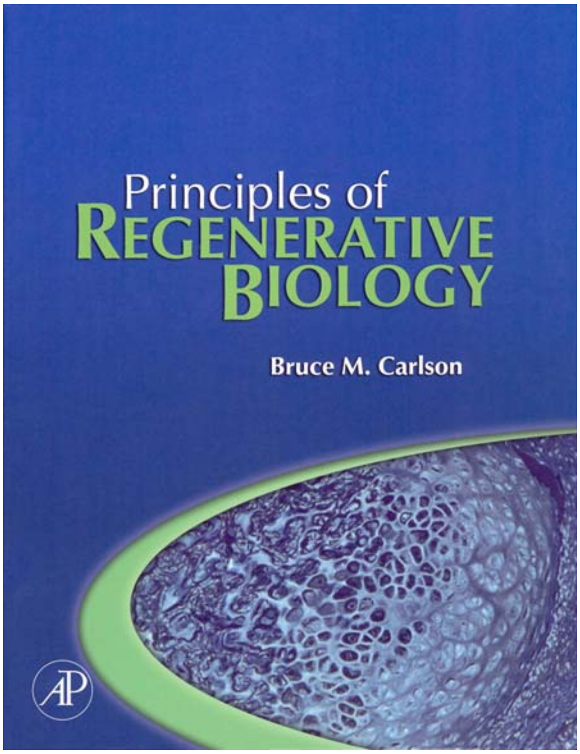

Figure 1. ***Principles of Regenerative Biology***

In the discussion of stem cells, there seems to be a certain vagueness about the distinction between tissue-specific stem cells (such as the familiar intestinal or hematopoietic stem cells) and those cells isolated from adult tissues that have high pluripotency comparable to that of embryonic stem cells. On page 246, there is the surprising remark that "true stem cells express the transcription factor Oct4." This seems to imply that the tissue-specific stem cells are not true stem cells. There is no discussion of the awkward problem that adult cells of high pluripotency do not easily fit into the normal account of development as it has become established in recent decades. This involves a hierarchy of developmental decisions leading to formation of the body plan, each made in response to an extracellular signal and each leading to a reduction in the range of developmental potency. According to this model, cells of high pluripotency should all have disappeared after the first few steps of development. However, they do seem to exist postnatally, and the existence of entities that do not fit into a well-established theory should be a cause for major attention.

In a work of such scope, it is perhaps unfair to complain about omissions. There are not many of them, but I think I would have discussed *Drosophila* imaginal disks and cockroach limbs at greater length. This is because work on *Drosophila* disks eventually enabled identification of the molecular basis of the "polar coordinate model," which will be familiar to those who can remember regeneration research in the 1980s. It was a macroscopic theory that explained the number, polarity, and pattern of complex regenerates arising from surgical manipulations on *Drosophila* disks, cockroach legs, and amphibian legs (French et al., 1976). The model was not wholly correct, but it was important in drawing attention to the role of positional value disparity in affecting whether regeneration occurred or not. After an initial burst of publicity, interest in it waned after a few years, and, rather surprisingly, the recent unraveling of its molecular basis in insects seems to have attracted little attention (Mito et al., 2002).

For some reason, regeneration research seems to be cursed with a significant number of high-profile published results that turn out to be irreproducible. Carlson tends to report these results simply as facts, and I feel he could have been more critical in some cases. One exception, in which he does question the textbook account, concerns the work of Singer showing that augmentation of the nerve supply can enable regeneration in otherwise nonregenerating frog limbs (Singer, 1954). Carlson several times indicates that these experiments were overinterpreted, that they did not lead to the formation of a real blastema, and that the regenerates were very incomplete.

Having read the book, we should be in a position to ask, "Are there, in fact, any *principles* of regeneration?" Carlson constantly emphasizes the complexity and diversity of regenerative phenomena, even to the extent that the same structure may be regenerated by different routes in different circumstances. So is it all just a mass of more cellular and molecular details with no real underlying principles? I like to feel that there are some principles in there somewhere. One key question, and the one that comes nearest to answering the lay person's query with which we started, concerns the nature of cellular dedifferentiation (although dedifferentiation is not found in all types of regeneration). I do feel that there must be something about the salamander at the cellular level which makes dedifferentiation easier than in mammals. We tend to think that this something will lie in the domain of chromatin structure, and this theme certainly unites regeneration and stem cell research where the nature of ES cell pluripotency, and its establishment in other cell types, is a very hot topic today.

Finally, even if we do understand the principles of regeneration, and as many of the details as we can manage to remember, will we ever be able to cause human limbs to regenerate? It is beginning to be possible to write down reasonable protocols on paper, although putting them into practice will take a long-term effort. In the end, scientific understanding may not be enough. Throughout medical science, there is an annoying tendency for many new treatments to be discovered by accident rather than by rational design, with the mechanism of action being discovered long after they have entered clinical practice. One of the existing products of regeneration research falls into this category. The electromagnetic bone stimulator has now been in the clinic for decades and is generally believed to improve the rate of healing of recalcitrant fractures, although Carlson wisely declines to commit himself on whether such devices are really effective.

For those who worry that the small slimy salamander limb seems a long way from our own appendages, perhaps the most optimistic element of the book is the reproduction in the final chapter of a photograph of a large alligator with a regenerating tail (from Han et al., 2005). An alligator tail has a similar crosssectional area to a human limb, suggesting that at least large size need be no impediment to effective regeneration.

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